Development of New Synthetic Method of the DFGH-ring of Physalin-Type Natural Products and SAR Study of the Pseudo-Natural Products

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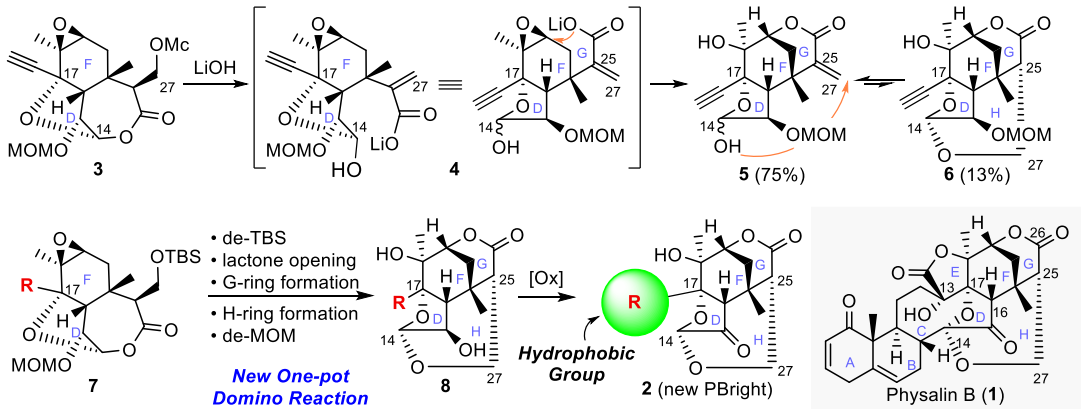
Keywords: Physalin; Steroid; Domino Reaction; Cascade Reaction; Structure-Activity Relationship

Physalins are steroidal constituents of *Physalis* plants and contain a complex, highly oxygenated fused-ring system. More than 30 physalin-type natural products have been isolated so far, and most of them possesses a highly fused and oxygenated DEFGH-ring structure like that of physalin B (**1**). The significance of the left-side (AB-ring) structure of **1** for biological activity is well established, but the importance of the right-side (D(E)FGH-ring) structure has long been unclear. Based on our previous study,[1)] we designed the simplified DFGH-ring structure **2** with the hydrophobic substituent (**R**) at C17, which may exhibit high inhibitory activity of NF-κB activation.

Since the right-side structure of physalin B (PBright) possesses a highly functionalized and fused ring structure, we required a robust synthetic route to **5** involving mild reaction conditions. In particular, the key GH-ring construction previously achieved via the base-mediated domino ring-opening/closure sequence (**3**→**4**→**5**→**6**)[2)], was problematic due to a bias of the equilibrium towards the more stable **5** rather than the desired **6**. During the synthetic study, we found an alternative synthetic route toward **2** via newly found domino sequence of **7** to directly give DFGH-ring compound **8**. Here we present the synthesis and SAR study of **2**.[3)]



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